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A Link between the Intrarenal Renin Angiotensin System and Hypertension in Autosomal Dominant Polycystic Kidney Disease

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Key Words
Polycystic kidney disease · Urinary angiotensinogen · Hypertension

Abstract
Background/Aims: Early onset of hypertension and its consequences account for the great majority of deaths in patients with autosomal dominant polycystic kidney disease (ADPKD). Renin-angiotensin system (RAS) components have been shown in ADPKD kidneys independent of systemic RAS. Thus, we examined the urinary angiotensinogen (UAGT) levels as a biomarker of intrarenal RAS status in ADPKD patients with/without hypertension and healthy subjects. ***Methods:*** Eighty-four ADPKD patients (43 with hypertension and 41 without hypertension) and 40 healthy controls were studied cross-sectionally. Patients with glomerular filtration rate <60 ml/min were excluded from the study. Hypertension was diagnosed with ambulatory blood pressure monitoring. Urinary and plasma concentration of angiotensinogen, spot urine microprotein and creatinine (UCre) levels were recorded for each participant. ***Results:*** UAGT/UCre levels were higher in hypertensive ADPKD patients (23.7 ± 8.4) compared with normotensive ADPKD patients (16.6 ± 5.2) and healthy controls (6.9 ± 3.3; $p < 0.001$). In univariate analysis, UAGT correlated with systolic blood pressure, diastolic blood pressure (DBP) and proteinuria. The independence of these correlations was analyzed in a regression model, and UAGT was shown to be significantly predicted by proteinuria and DBP. ***Conclusion:*** Intrarenal RAS activation which is monitored by UAGT levels clinically may be a harbinger of hypertension and kidney disease in ADPKD patients.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary reason of chronic kidney disease and accounts for 8–10% of patients with end-stage renal disease (ESRD) [1]. Hypertension is very common in ADPKD and occurs in approximately 60% of patients before the decline of the glomerular filtration rate [2, 3]. Early onset of hypertension is a well-known entity in ADPKD patients compared to the general population [4]. Furthermore, hypertension is associated with rapid progression to ESRD and increased cardiovascular events [5, 6]. Cardiovascular disease due to hypertension remains the main cause of mortality in ADPKD patients [7]. The mechanism of hypertension has not as yet been fully clarified; the widely accepted hypothesis is that cyst-induced renal ischemia causes stimu-

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lation of the renin-angiotensin system (RAS), since it was shown that the degree of renal cystic enlargement correlated with the presence of early hypertension in ADPKD [8]. Although the role of systemic RAS has been postulated, no consistent data have demonstrated the association between blood pressure and activation of circulating RAS in ADPKD [9–14]. Emerging evidence has demonstrated the importance of intrarenal RAS that is regulated independently of systemic RAS and its role in the development of hypertension, renal diseases and glomerulosclerosis [15, 16]. Taken together, the focus of interest on hypertension has shifted towards the role of intrarenal RAS in ADPKD since it has been demonstrated that cyst-derived cells express renin mRNA, suggesting local renin synthesis. Likewise, it has been established that all the components of RAS were also present in the cysts and dilated tubules of ADPKD kidneys [17, 18].

Angiotensinogen (AGT) is the only substrate for renin, which is the rate-limiting enzyme of RAS. Plasma AGT is produced by the liver, but cannot be filtrated through the glomerular membrane due to its high molecular weight [16, 19]. Recently, it was reported that the urinary excretion rates of AGT provide a specific index of the intrarenal RAS status in angiotensin II (ANG II)-dependent hypertensive rats [20–22]. It was developed as a direct quantitative method to measure urinary AGT (UAGT) using human AGT enzyme-linked immunosorbent assay (ELISA) [23]. This method has been used to measure the urinary excretion rates of AGT, and AGT has been widely accepted as a biomarker for the intrarenal activity of RAS in patients with hypertension [24] chronic kidney disease [25], and diabetic nephropathy [26].

However, the putative role of intrarenal RAS has not been well studied in ADPKD patients. With the hypothesis other than systemic RAS activation due to cyst compression and subsequent fluid retention, decreased nitric oxide generation and hyperuricemia, we examined the relationship of intrarenal RAS status by demonstrating UAGT measurements in hypertensive ADPKD patients compared to normotensive ADPKD patients and normotensive subjects.

Subjects and Methods

Study Population

Between February 2012 and November 2012, 105 ADPKD patients were registered by Kayseri Erciyes University School of Medicine and Ankara Gulhane School of Medicine from the Turkish Society of Nephrology Polycystic Kidney Disease Working Group Registry and were evaluated for the study. The study was approved by the ethics committees and Local Hospital Review Committees of both Universities. These two academic medical centers serve an area of 5,000,000 residents. All of the participants were included after signing written informed consent forms. The diagnosis of ADPKD was confirmed by a positive family history and the presence of 5 or more renal cysts on renal ultrasound, distributed over both kidneys. The demographic characteristics (e.g. gender, age, education status and smoking history), renal manifestations (e.g. hematuria, urinary system infection, urinary tract stones and renal replacement therapy) and cardiovascular manifestations (e.g. hypertension and mitral valve prolapse) were recorded on the web-based data recruitment forms. The patients were also screened for hypertension by ambulatory blood pressure monitoring because of the diagnosis of hypertension. Finally, 84 ADPKD patients with and without hypertension and 40 healthy subjects were eligible for the study. While 27 patients were taking angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) for hypertension, 16 patients were receiving non-ACE-I/ARBs (9 calcium channel blockers, 5 beta-blockers and 1 alpha-blockers) in the hypertensive ADPKD group. A flow diagram of the study design is depicted in figure 1.

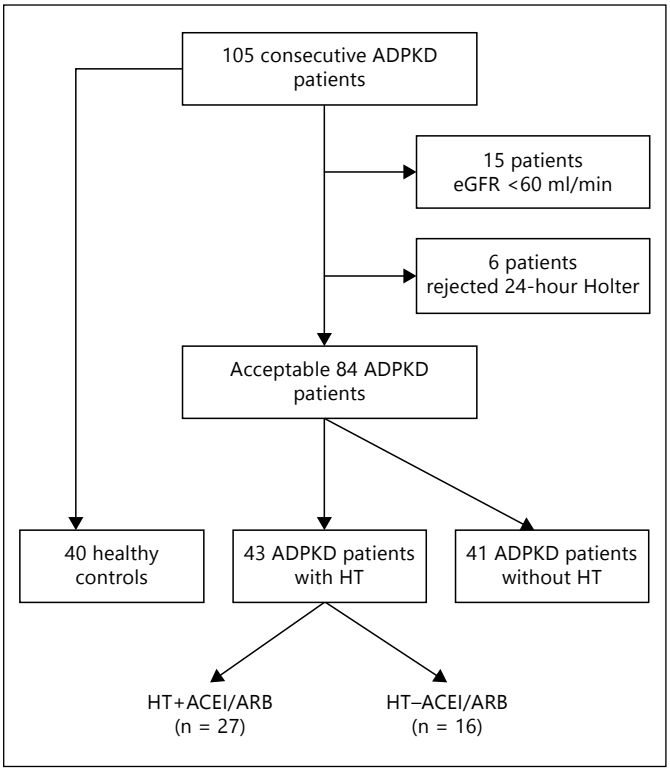

Fig. 1. Diagram showing the flow of the study. HT = Hypertension.

The enrolled patients were reevaluated in terms of systemic inflammation, urinary tract stones and infection. None of the patients showed any signs of either stones or infection. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) formula: MDRD = 186 × [serum creatinine (mg/dl)] – 1.154 × age – 0.203. A correction factor of 0.742 was used for women [27].

Table 1. Demographic, clinical and laboratory features of patients and controls

Parameter	ADPKD patients without HT (n = 41)	ADPKD patients with HT (n = 43)	Healthy controls (n = 40)	p
Age, years	36.6±10.9	36.6±9.4	36.1±9.8	0.96
Females/males	16/25	11/32	13/27	0.42[a]
Serum glucose, mg/dl	82.1±12.4	83.4±13.0	82.6±12.5	0.89
Total cholesterol, mg/dl	184.1±37.1	178.7±29.8	168.5±36.3	0.12
HDL cholesterol, mg/dl	38.9±8.6	37.6±7.3	35.7±7.3	0.18
LDL cholesterol, mg/dl	119.8±30.8	112.4±25.1	104.3±37.8	0.09
Plasma triglyceride, mg/dl	149.5±49.8	151.5±61.8	142.1±78.5	0.78
Body mass index, kg/m^2	22.3±3.7	23.0±3.4	22.6±3.7	0.67
Serum uric acid, mg/dl	6.5±1.7	7.3±1.5	5.8±1.1	0.22
Serum calcium, mg/dl	8.9±0.5	8.9±0.47	8.9±0.45	0.91
Serum phosphorus, mg/dl	3.8±0.8	3.7±0.8	3.8±0.7	0.87
eGFR, ml/min per 1.73 m^2	88.6±12.9	85.3±10.8	90.8±9.2	0.18
UAGT/UCre, μg/g	16.6±5.2[b]	23.7±8.4[b, c]	6.9±3.3	<0.001

[a] p = χ^2 value; [b] p < 0.05 vs. healthy controls; [c] p < 0.05 vs. ADPKD patients without hypertension.

Biochemical and Urine Measurements

Blood samples were taken from the vein in the antecubital fossa with subjects in a seated position following 20-min rest and after 12 h of fasting. Serum concentrations of sodium, potassium, creatinine, and urinary concentrations of sodium and microprotein were measured by standard methods in our clinical laboratory in the Hospital of Erciyes University School of Medicine. Morning spot urine samples were collected from all patients and controls to measure UAGT and urinary microprotein-to-creatinine ratio (UPro/UCre) levels. Urinary concentrations of microprotein and creatinine were measured by an automated machine (Abbott Diagnostics, Architect c8000, USA) with adequate kits.

Urinary and plasma concentration of AGT was measured with human AGT ELISA kits (Ref. E90797 Hu; Uscn Life Science Inc., Wuhan, China). The concentration of UAGT was adjusted with same sample urine creatinine.

Ambulatory Blood Pressure Measurements

The 24-hour blood pressure monitoring was performed using a Del Mar Medical Pressurometer Model P6 (Del Mar Reynolds, Irvine, Calif., USA), and the results were assessed using the manufacturer's computer software. Ambulatory measurements were conducted once every 15 min from 7 a.m. until 11 p.m., and once every 30 min from 11 p.m. until 7 a.m. Evaluation was performed taking the mean values of day and night blood pressures into account. Hypertension was considered to be present if the systolic blood pressure (SBP) was ≥140 mm Hg and/or diastolic blood pressure (DBP) was ≥90 mm Hg, or if the individual was taking antihypertensive medication.

Statistical Analysis

Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test. We report continuous data as mean and standard deviation or median. We compared continuous variables using the Student's t test. Categorical variables were summarized as percentages and compared with the χ^2 test. One-way ANOVA and Dunnett's test were used to compare group means. Pearson correlation coefficients were calculated to examine the degree of association between variables. A p value <0.05 was considered as significant. In multivariate analysis, variables for which the unadjusted univariate p value was <0.10 in linear regression analysis were included. We reduced the model by using backward elimination multivariate linear regression analysis and compared remaining risk markers using likelihood ratio tests. A p value <0.05 was considered as significant, and the confidence interval was set to 95%. All statistical analyses were performed using SPSS v15 (SPSS Inc., Chicago, Ill., USA).

Results

The demographic, clinical, and laboratory characteristics of the study population are shown in table 1. There were no significant differences between the three groups in terms of baseline parameters. However, UAGT/UCre levels were higher in hypertensive ADPKD patients (23.7 ± 8.4) compared with normotensive ADPKD patients (16.6 ± 5.2) and healthy controls (6.9 ± 3.3) (p < 0.001).

In subgroup analysis, hypertensive ADPKD patients were divided into two groups in terms of medications taken, i.e. RAS blocker or not (table 2). There were no significant differences in terms of plasma AGT, average 24-hour SBP and average 24-hour DBP, but levels of UPro/UCre and UAGT/UCre were lower in the RAS blockade group, compared with the non-RAS blockade group (fig. 2).

Additionally, 24-hour ambulatory blood pressure monitoring confirmed the status of all study participants (table 3).

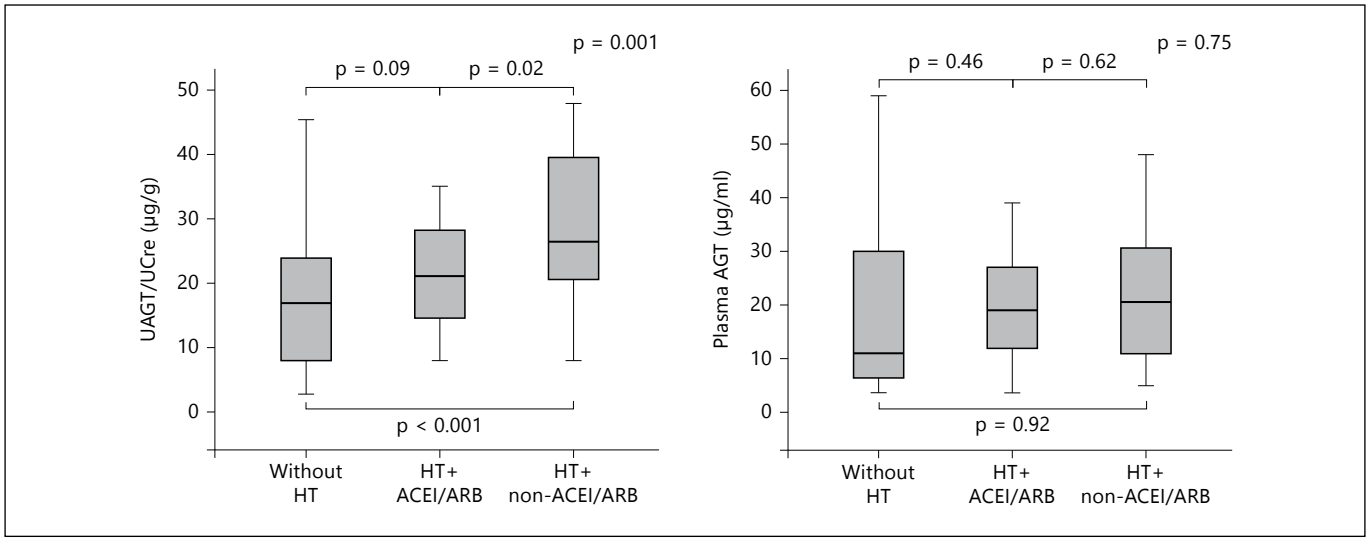

Fig. 2. UAGT/UCre and plasma AGT levels in hypertensive patients with/without RAS blockade and in normotensive subjects.

Table 2. Subgroup analysis of ADPKD patients with hypertension

Parameter	ADPKD patients with hypertension (n = 43)		
	ACEI or ARB (n = 27)	other (n = 16)	p
UPro/UCre	0.44±0.16	0.72±0.22	0.02
Plasma AGT, μg/ml	24.1±8.4	21.3±11.8	0.61
UAGT/UCre, μg/g	21.0±8.2	28.4±12.1	0.02
Average 24-hour SBP, mm Hg	121.6±8.4	124.8±7.8	0.24
Average 24-hour DBP, mm Hg	81.8±7.8	84.3±6.4	0.36

The univariate correlations of selected markers in all the 124 study participants are listed in table 4. In the whole cohort, UAGT correlated with SBP ($r = 0.24$, $p = 0.008$), DBP ($r = 0.396$, $p < 0.001$) and proteinuria ($r = 0.541$, $p < 0.001$; fig. 3) but not with high-sensitivity C-reactive protein (hs-CRP; $r = 0.043$, $p = 0.69$), LDL cholesterol ($r = 0.98$, $p = 0.28$) and uric acid ($r = 0.162$, $p = 0.068$; table 4). Meanwhile, plasma AGT was not correlated with SBP, DBP, hs-CRP, LDL cholesterol, proteinuria and uric acid.

The independence of multiple correlations was analyzed with multivariate linear regression analyses. The original model included eGFR, UPro/UCre, uric acid, average 24-hour SBP and average 24-hour DBP. In all subjects, UAGT was independently predicted by UPro/UCre ($\beta = 17.641$, $p < 0.001$), average 24-hour DBP ($\beta = 0.411$, $p = 0.001$) but not uric acid ($\beta = 0.482$, $p = 0.055$; table 5).

Discussion

The present study was undertaken to explore further the potential role of UAGT as an important index of intrarenal RAS status in hypertension associated with ADPKD. This study proposes three major findings in patients with ADPKD and preserved renal function. First, UAGT/UCre levels were significantly greater in patients with hypertensive ADPKD compared with both normotensive ADPKD patients and normotensive healthy subjects. Additionally, plasma levels of AGT were not significantly different in these three groups. Secondly, UAGT/UCre and UPro/UCre levels were significantly greater in hypertensive ADPKD patients without RAS blockade. Importantly, hypertensive patients with RAS blockade did not have this augmentation. Thirdly, UAGT/UCre levels were significantly correlated with UPro/UCre levels and 24-hour DBP.

Hypertension develops earlier in ADPKD patients when they are compared with the general population [4]. Progressing to end-stage renal failure without any intervention and cardiovascular problems due to hypertension are the prominent features of ADPKD [3, 5, 6]. Hypertension, which is directly related to cardiovascular problems, accounts for the great majority of deaths in this population [3, 7]. Thus, investigators have focused on the underlying reason for hypertension in this population over the years. Although the precise mechanism of hypertension in early ADPKD has not yet been elucidated, early vascular changes have been shown in normotensive

Table 3. Data from ambulatory blood pressure measurement of the study subjects

Parameter	ADPKD patients without HT (n = 41)	ADPKD patients with HT (n = 43)	Healthy controls (n = 40)	p
Average 24-hour SBP, mm Hg	113.4±5.4	124.0±8.0[a, b]	110.8±6.4	<0.001
Average daytime SBP, mm Hg	119.4±6.9	127.3±8.1[a, b]	117.6±8.1	<0.001
Average night-time SBP, mm Hg	107.4±5.3	120.8±8.2[a, b]	104.1±6.3	<0.001
Average 24-hour DBP, mm Hg	74.2±3.8	83.8±6.9[a, b]	71.8±4.5	<0.001
Average daytime DBP, mm Hg	79.1±4.8	86.0±6.9[a, b]	76.9±5.3	<0.001
Average night-time DBP, mm Hg	69.8±4.6[a]	81.6±7.1[a, b]	67.0±4.3	<0.001
Average 24-hour mean BP, mm Hg	87.4±4.0[a]	97.2±5.0[a, b]	84.8±4.6	<0.001
Average daytime mean BP, mm Hg	92.6±4.7	99.7±5.1[a, b]	90.4±5.4	<0.001
Average night-time mean BP, mm Hg	82.3±4.4[a]	94.6±5.3[a, b]	79.2±4.4	<0.001

BP = Blood pressure; HT = hypertension. [a] $p < 0.05$ vs. healthy controls; [b] $p < 0.05$ vs. ADPKD patients without HT.

Table 4. Univariate correlates of selected markers in all 124 study participants

	Average 24-hour SBP (mm Hg)		Average 24-hour DBP (mm Hg)		LDL (mg/dl)		hs-CRP (mg/dl)		UPro/UCre		Uric acid (mg/dl)	
	r	p	r	p	r	p	r	p	r	p	r	p
Age (years)	0.10	0.25	0.16	0.86	0.21	**0.017**	–0.07	0.51	–0.57	0.528	–0.85	0.34
UAGT/UCre (μg/g)	0.24	**0.008**	0.396	**<0.001**	0.98	0.28	0.043	0.69	0.541	**<0.001**	0.162	0.068
Plasma AGT (μg/ml)	0.12	0.19	0.11	0.19	–0.63	0.45	–0.02	0.84	0.37	0.68	0.018	0.841
eGFR (ml/min/1.73 m^2)	–0.12	0.18	–0.67	0.46	0.06	0.51	–0.14	0.18	–0.55	0.542	–0.07	0.41

Values in bold are significant ($p < 0.05$).

ADPKD patients prior to the development of hypertension [28]. Recently, we demonstrated arterial stiffness and inflammation in normotensive ADPKD patients with preserved kidney function that might be a contributing factor for early onset of hypertension [29]. Nevertheless, the pathogenesis of hypertension in ADPKD and the trigger factor remains unclear.

Increased activity of RAS and extracellular volume expansion due to cystic enlargement are present in ADPKD and are thought to be responsible for the development of hypertension [2, 8, 12]. Supporting this widely adopted hypothesis, it has been recently shown that kidney volume is associated with early onset of hypertension and disease severity [30]. While plasma renin activity and plasma aldosterone levels have been found higher in both hypertensive and normotensive ADPKD patients [8, 31], some investigators showed plasma renin activity were similar in ADPKD patients compared with controls [9–11]. Based on these reports, the role of systemic RAS activation in the development of hypertension in ADPKD remains controversial. Moreover, indirect evidence is available to confirm the activation of the RAS in ADPKD since it has been demonstrated that treatment with RAS blockers decreases mean arterial pressure, renal vascular resistance and filtration fraction significantly more in hypertensive ADPKD patients than in healthy normotensive subjects [8, 32]. In contrast, it was shown that blood pressure and the hormonal responses of RAS after administration of RAS blockers were not different in hypertensive ADPKD patients and essential hypertensive subjects [11]. Depending on these conflicting results, the focus of interest on RAS has recently shifted towards the role of intrarenal RAS. Torres et al. [17] first reported the relationship between renin secretion and cysts and dilated tubules in ADPKD kidneys. Likewise, Loghman-Adham et al. [18] demonstrated that cyst-lining epithelia can synthesize all the components of the RAS; thus, the production and secretion of ANG II have been shown in

Table 5. Multiple regression analysis backward method for UAGT/UCre

	UAGT/UCre, μg/g		
	β	SE	p
Intercept	–27.877	9.14	0.003
UPro/UCre	17.641	2.843	<0.001
Average 24-hour DBP (mm Hg)	0.411	0.115	0.001
Uric acid (mg/dl)	0.978	0.482	0.055

The original model included eGFR, UPro/UCre, uric acid, average 24-hour SBP and average 24-hour DBP. Adjusted $r^2 = 0.41$. SE = Standard error.

ADPKD kidneys. Intrarenal RAS that is regulated independently of circulating RAS has been reported; subsequently, investigators have demonstrated that increased activity of the intrarenal RAS rather than the systemic RAS could be responsible for many forms of hypertension [15, 16, 24, 33]. In conclusion, the evaluation of intrarenal RAS activation has become a means to understand the pathophysiological mechanism of hypertension and renal diseases.

It has been recently demonstrated by both experimental and clinical studies that UAGT levels reflect intrarenal ANG II activity. AGT is the only known substrate for renin, which is the rate-limiting enzyme of the RAS. AGT level is close to the Michaelis-Menten constant for renin, thus AGT levels can also control the activity of the RAS. In addition, plasma AGT is produced by the liver, but cannot be filtrated through the glomerular basement membrane due to its high molecular weight. Consequently, it has been suggested that UAGT reflects locally produced AGT that was secreted from proximal tubular cells. Kobori et al. [15, 16, 20–22] demonstrated that UAGT, independent of plasma AGT, provides a specific index of intrarenal RAS status in hypertensive rats, and they generated an ELISA method for monitoring UAGT levels in human studies.

Although the presence of intrarenal RAS status was demonstrated in ADPKD, its relation with hypertension has not been well studied in clinical trials. Intrarenal RAS activation has recently become more popular than systemic RAS to explain the development of hypertension, and UAGT is a clinically useful marker for monitoring intrarenal RAS status [22, 34]. Moreover, increased UAGT levels have been shown as an indicator of intrarenal RAS status in different populations such as those with essential hypertension, chronic kidney disease, diabetes

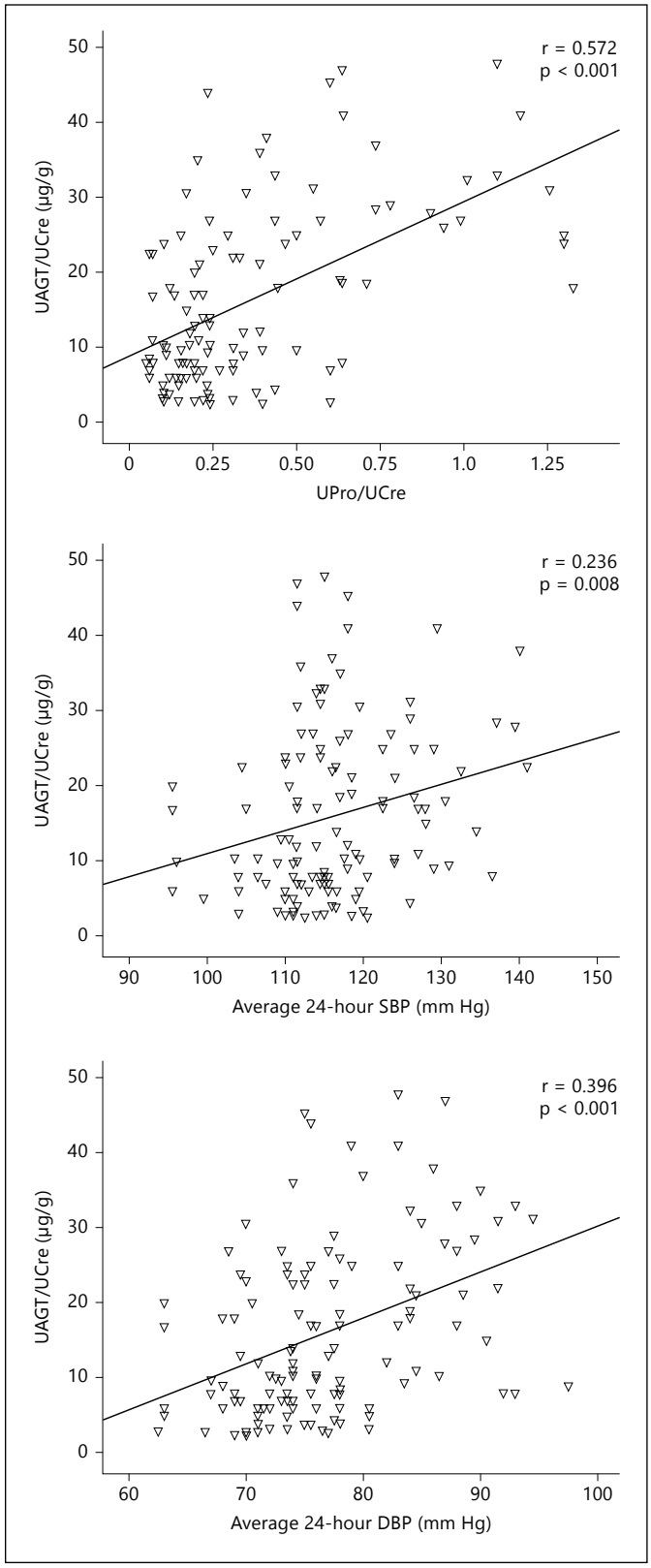

Fig. 3. Univariate regression analyses for UAGT/UCre levels with UPro/UCre ratio, SBP and DBP.

mellitus, IgA nephropathy, amyloidosis, and hypertensive renal transplant recipients [24, 26, 33, 35–37]. Therefore, we aimed to investigate intrarenal RAS activation by UAGT/UCre measurements and its association with hypertension in an ADPKD population. To the best of our knowledge, this is the first study to evaluate the relationship between UAGT and hypertension in ADPKD. Herein, we showed that UAGT/UCre levels are significantly more increased in hypertensive ADPKD patients than both healthy subjects and normotensive ADPKD patients. According to the results, it has been demonstrated that UAGT levels increased in normotensive ADPKD patients compared with healthy subjects even though their blood pressure levels did not differ significantly. Depending on these findings, it is plausible that intrarenal RAS activation which may result in the development of hypertension is a specific problem of ADPKD patients. We suggest that hypertension could be a result of intrarenal RAS activation in the ADPKD population; thus, increased levels of UAGT could be associated indirectly with blood pressure levels. On the other hand, treatment with RAS blockers attenuated augmentation of UAGT levels in hypertensive ADPKD patients, which was also investigated in a previous study in essential hypertensive patients [24]. It is possible that RAS blockers might be useful in slowing kidney disease progression by preventing interstitial inflammation and fibrosis by blocking intrarenal RAS activation, in addition to their antiproteinuric effect in those with hypertensive ADPKD.

Another important finding of this study was the significant positive correlation between UAGT/UCre and UPro/UCre ratios in ADPKD patients. Previous studies on renal diseases have shown conflicting results. However, it has been shown that UPro/UCre levels were correlated with proteinuria in patients with chronic glomerulonephritis and chronic kidney disease [25, 38]. In contrast, it has been reported that UAGT/UCre levels were similar in patients with minimal change nephropathy and control subjects, even though patients with minimal change nephropathy had severe proteinuria and it was stated that UAGT was not a specific result of proteinuria [39]. On the other hand, it has been demonstrated that increased UAGT levels precede increased urinary protein levels in type 1 diabetes [40]. The present study suggested that urinary protein excretion could be a consequence of the intrarenal RAS activation, which is demonstrated by UAGT levels, and it is indirectly specific to ADPKD patients. Hence, further prospective studies are required to explore this issue.

The major limitations of the current study are its cross-sectional design and small sample size. Second, total kidney volume relates to cystic enlargement and pressure on the renal vasculature that result in the reduction in renal plasma volume via activation of the systemic RAS [2, 3]. We could not measure total kidney volume and renal plasma flow to assess their effect on hypertension in ADPKD patients, which is important as they are generally considered as better predictive indicators than UAGT/UCre levels. However, we measured plasma AGT levels and did not find a significant difference between hypertensive ADPKD patients and the other two groups. Obviously, further studies with a larger number of patients and a longer observation period are needed to address this issue.

In conclusion, the present study suggests that UAGT/UCre is a potential novel biomarker of intrarenal RAS status in hypertensive ADPKD patients. UAGT/UCre levels may be an applicable and useful index to predict future cardiovascular complications and progressive kidney disease in ADPKD patients. Additionally, we suggest that RAS-blocking agents are useful in blocking intrarenal RAS activation, but further studies are needed to clarify their efficiency in this blockade. Finally, this study provided a background for longer trials to test the role of intrarenal RAS status in ADPKD patients.

Disclosure Statement

None.

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